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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/577,059	05/22/2000	William J. Curatolo	PC8626BJTJ	2926

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EXAMINER	
CHOI, FRANK I	
ART UNIT	PAPER NUMBER
1616	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/577,059	CURATOLO ET AL.	
	Examiner	Art Unit	
	FRANK I. CHOI	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 June 2006*.

2a)☒ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *72-95 and 125-148* is/are pending in the application.

4a) Of the above claim(s) *77-79,87-92,130-132 and 140-145* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *72-76,80-86,93-95,125-129,133-139 and 146-148* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/6/2007 has been entered.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 72-76,80-86,93-95, 125-129, 133-139, and 146-148 are rejected under 35 U.S.C. 103(a) as being unpatentable over Curaltolo et al. (US Pat. 5,605,889) in view of Handsfield et al., Urquhart (US Pat. 4,851,231), Edgren (US Pat. 4,522,625) , Etienne et al. (US Pat. 4,755,385) and Periti et al. (Abstract) for the reasons of record set forth in the prior Office Action and the further reasons below.

Curatolo et al. (U.S. Pat. No. 5,605,889) teaches a dosage form of azithromycin which can be administered to a mammal. The dosage form is composed of from about 25mg to 3 grams of azithromycin (col. 4, lines 51-54). The dosage forms can further be adjusted depending on the size of the animal subject being treated (Id. at lines 54-57). During in-vitro analysis utilizing USP-2 dissolution apparatus under the conditions of 900ml approx. 0.1M dibasic sodium phosphate buffer, pH 6.0, 37°C, with paddles turning at 100rpm, the azithromycin dosage form

of Curatolo et al. exhibits 90% dissolution within 15 minutes when an amount of the dosage form is equivalent to 200mg (col. 5, lines 27-35). When comparing dosage forms of different types, in vitro dissolution rates should correlate with in vivo dissolution rates (col. 5, lines 57-60). It is further taught that tablet blends of the dosage form maybe dry or wet granulated before tableting (col. 7, lines 51-52), such granules dried, blended and pressed to make the dosage form (see Example 8, col. 16). The tablet blends can be film-coated with hydroxypropyl methylcellulose (col. 7, line 65-col. 8, line 2). Additionally, a formulation is taught wherein the average percent azithromycin dissolved at 30 minutes was 76% (Column 11, Example 1).

Handsfield et al. ("Single-dose azithromycin versus ceftriaxone for treatment of uncomplicated gonorrhea") teaches that 2.0 grams of azithromycin administered for treatment of uncomplicated gonorrhea, cured 41/41 men and 4/4 women, however caused nausea in 34% and diarrhea in 14% (see abstract).

It is taught in the prior art, as shown by Urquhart et al. (U.S. Pat. No. 4,851,231), that certain drugs should not be administered to the stomach, for example drugs that are digested or decomposed in the acidic environment of the stomach such as the antibiotic erthyromycin and drugs that induce nausea and vomiting (col. 1, lines 38-43). Urquhart et al. teaches the need for a delivery system which avoids administering a drug in the stomach, but rather administers a drug in a therapeutically effective amount in the intestine over time (col. 1, lines 58-63).

Edgren (U.S. Pat. No. 4,522,625) teaches a dispenser for releasing drug formulations in the gastrointestinal tract. The dispenser of Edgren allows for the delivery of drugs at rates precisely controlled by the dispenser, which are rates in response to the biological environment (col. 1, lines 44-51). The dispenser is comprised of a body having a wall that surrounds an

internal compartment. A passageway in the wall connects the interior of the dispenser with the exterior (col. 2, lines 39-47). The dispenser can be made for oral use, such use being useful for releasing in the gastrointestinal tract either a locally or systemically acting drug over a prolonged period of time (col. 3, lines 43-46). The oral dispenser can have various shapes such as round or capsule shaped (Id. at lines 48-49). Enteric materials can be blended with a semi-permeable polymer for forming the wall of the dispenser, such enteric materials including hydroxypropyl methylcellulose phthalate (col. 4 lines 35-37 and lines 64-65). The passageway includes apertures, orifices, bores, holes, and the like through the wall (col. 5, lines 32-34). The expression drug can include antibiotics such as erythromycin (col. 5, line 66 and col. 6, line 4).

Etienne et al. disclose many macrolide antibiotics, such as erythromycin and AS-E 136 are sensitive to acidic media and are usually destroyed by the action of gastric juices (Column 1, lines 34-38). It is disclosed that it is well known to compress active substances with suitable excipients to form a tablet and coat a tablet with gastric juice-resistant lacquers such as cellulose acetate phthalate or hydroxyl-propylmethylcellulose phthalate which after leaving the stomach the lacquer dissolves in the intestinal juices and the active substance is dissolved and resorbed (Column 2, lines 25-53). It is disclosed that resistant to gastric juices means that the preparation should release virtually no active substance for a period between 30 minutes and 2 hours and having a pH solubility of between 5.5 and 6.8 or which releases the active substance at a pH of between 5.5 and 6.8, preferably, between 6.0 and 6.4 (Column 4, lines 5-10,60-68, Column 5, lines 1-6). Tests are performed using USPXX apparatus at 100 rpm at pHs of 1.2, 4.5, 6.0, 6.2, 6.4 and 6.5 (Examples 1-8).

Periti et al. discloses that azithromycin is acid unstable (although exhibiting increased acid stability over older macrolide antibiotics) (Abstract).

The prior art discloses that azithromycin is effective for treating uncomplicated gonorrhea and drugs such as erythromycin, that induce nausea and vomiting should be administered to the intestine over time. The difference between the prior art and the claimed invention is that the prior art does not expressly disclose the in vitro criteria of Q0.25, Q1, Q2, Q4 and Q6 as determined by the claimed testing parameters. However, the prior art suggests the same as the prior art discloses that although erythromycin and azithromycin do have their differences, both erythromycin and azithromycin exhibit adverse gastric effects and are acid unstable (although azithromycin does have increased acid stability over erythromycin) and that resistant to gastric juices means that the preparation should release virtually no active substance for a period between 30 minutes and 2 hours and having a pH solubility of between 5.5 and 6.8 or which releases the active substance at a pH of between 5.5 and 6.8, preferably, between 6.0 and 6.4. As such, it would have been well within the skill of and one of ordinary skill in the art would have been motivated to control the release of azithromycin to be released at least 30 minutes after ingestion so as to avoid adverse gastric effects and any acid instability by using an enteric coating which dissolves preferably at a pH of between 6.0 and 6.4. As such, one of ordinary skill in the art would expect that for enteric coatings which dissolve at pHs of greater than 6.0 that substantially no active agent will be released until the pH of the surrounding media, whether in vitro or in vivo, is at the appropriate pH. As such, such a dosage form will meet the criteria set forth in the claims.

The Examiner has duly considered Applicant's arguments but deems them unpersuasive for the reasons set forth in the prior Office Action and the further reasons below.

The Supreme Court in *KSR International Co. v. Teleflex Inc.*, held the following:

(1) the obviousness analysis need not seek out precise teachings directed to the subject matter of the challenged claim and can take into account the inferences and creative steps that one of ordinary skill in the art would employ;

(2) the obviousness analysis cannot be confined by a formalistic conception of the words teaching, suggestion and motivation, or by overemphasis on the importance of published articles and the explicit content of issued patents;

(3) it is error to look only the problem the patentee was trying to solve-any need or problem known in the filed of endeavor at the time of invention and addressed by the prior art can provide a reason for combining the elements in the manner claimed;

(4) it is error to assume that one of ordinary skill in the art in attempting to solve a problem will be led only to those elements of prior art designed to solve the same problem-common sense teaches that familiar items may have obvious uses beyond their primary purposes, and in many cases one of ordinary skill in the art will be able to fit the teachings of multiple patents together like pieces of a puzzle (one of ordinary skill in the art is not automaton);

(5) it is error to assume that a patent claim cannot be proved obvious merely by showing that the combination of elements was "obvious to try". *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1396, 1397 (U.S. 2007).

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on

combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Further, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

The mere fact that there are non-controlled formulations in the market does not refute the fact that acid sensitivity is a motivation for formulating a controlled release formulation. There could be any of a number of reasons why the manufacture selected non-controlled formulations; this does not mean that acid sensitivity is not a valid motivation to formulate controlled release formulations. For example, aspirin is sold as non-controlled release and controlled release formulations; the fact that aspirin is sold in a non-controlled release formulation does not make enteric coated aspirin any less obvious. The Applicant's reason or motivation to prepare a controlled release formulation does not have to be the same as the motivation in the prior art. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. See, e.g., *In re Kahn*, 441 F.3d 977, 987, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006) (motivation question arises in the context of the general problem confronting the inventor rather than the specific problem solved by the invention); *Cross Med. Prods., Inc. v. Medtronic Sofamor Danek, Inc.*, 424 F.3d 1293, 1323, 76 USPQ2d 1662, 1685 (Fed. Cir. 2005) ("One of ordinary skill in the art need not see the identical problem addressed in a prior art reference to be motivated to apply its teachings."); *In re Linter*, 458 F.2d 1013, 173 USPQ 560

(CCPA 1972); *In re Dillon*, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1990), cert. denied, 500 U.S. 904 (1991). As such, whether or not one of ordinary skill in the art would have recognized that azithromycin side-effects were locally mediated does not overcome the motivation in the prior art. The prior art disclosed that Azithromycin caused nausea, as such, as an additional reason, one of ordinary skill in the art would have delayed release until after the drug passed through the stomach.

The Applicant's citation to Fiese et al. does not overcome the rejection. Fiese et al. clearly indicate that azithromycin is subject to acid degradation although to a far less extent than erythromycin. Further, Fiese et al. only indicated that azithromycin may not need to be in an enteric formulation. They did not conclude that in fact azithromycin does not need to be in an enteric formulation. Since there is some acid degradation, instead of having to adjust dosages to account for differences in acid content of the stomach and stomach transit times, it would be simpler to simply avoid the release in the stomach altogether. Further, since azithromycin as indicated above causes nausea, this would be an independent reason to enteric coat azithromycin.

The Applicant argues that the claims do not embrace enteric dosage forms. However, the claims, in fact, do not exclude enteric dosage forms. The claims recite less than or equal with respect to the amounts at the identified Q time periods and not more than 70% of its contained azithromycin within one half hour. Said limitations encompass releases of amounts equal or close to zero, as such, enteric coatings are encompassed by the claimed invention.

Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because every element of the invention has been collectively taught by the combined teachings of the references.

Terminal Disclaimer

The terminal disclaimer filed on 8/6/2007 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of 6,068,859 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Conclusion

A facsimile center has been established in Technology Center 1600. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier number for accessing the facsimile machine is 571-273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Choi whose telephone number is (571)272-0610. Examiner maintains a compressed schedule and may be reached Monday, Tuesday, Thursday, Friday, 6:00 am – 4:30 pm (EST).

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's Supervisor, Johann R. Richter, can be reached at (571)272-0646. Additionally, Technology Center 1600's Receptionist and Customer Service can be reached at (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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July 3, 2008

/Johann R. Richter/
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